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Role of thyroid ultrasound in the diagnostic evaluation of thyroid nodules

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Thyroid ultrasound (US) features associated with malignancy in thyroid nodules are microcalcifications, hypoechogenicity, irregular margins or absent halo sign, solid aspect, intranodular vascularization, and shape (taller than wide).These patterns, taken singly, are poorly predictive. When they are simultaneously present the specificity increases at the expense of sensitivity. US elastography (USE) is a powerful new diagnostic tool that assesses hardness as an indicator of malignancy in thyroid nodules. USE has high specificity and sensitivity independent of the nodule size, and this predictive value is maintained in follicular lesions. Available data suggest that USE is the best available non-invasive tool comparable to fine-needle aspiration (FNA) for the evaluation of thyroid nodules, provided that the nodule is solid and devoid of coarse calcifications. Thus, conventional US retains its importance for selecting nodules in which USE is predictive. In conclusion, USE has great potential as a new tool for the diagnosis of thyroid cancer, especially in nodules with indeterminate cytology.

Key words: thyroid; thyroid ultrasound; US elastography; thyroid nodules.

Thyroid ultrasound (US) is a widespread technique that is used as a first-line diagnostic procedure in thyroid disease. Its usefulness is widely recognized for detecting and characterizing nodular thyroid disease. Thyroid nodules are common worldwide, their prevalence being dramatically increased in iodine-deficient areas. The great majority of nodules are benign, less than 5% of them being malignant.[1–9] Cytological examination of material obtained by fine-needle aspiration (FNA), due to its high sensitivity and specificity, is the best single test for differentiating between malignant and benign

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thyroid lesions.[10–13] As compared with FNA, thyroid US has the advantage of being a non-invasive procedure and of giving immediate information; thus several studies have been performed to establish its ability to differentiate between benign and malignant lesions.[14–17]

In the assessment of thyroid nodules, clinical evaluation is also very important. In particular, as reported in a recent consensus, a firm or hard consistency is associated with an increased risk of malignancy.[18–20] However, this clinical parameter is highly subjective and dependent on the experience of examiner. US elastography is a newly developed dynamic technique, based upon the principle that the softer parts of tissues deform easier than the harder parts under compression by an external force. This elasticity can be assessed by measuring the degree of distortion of the US beam.[21,22] Malignant lesions are often associated with changes in the mechanical properties of a tissue, and US elastography has been employed to differentiate cancers from benign lesions in prostate, breast, pancreas and lymph nodes.[23–29] In the evaluation of breast lesions Tan et al [30] found a good correlation between elasticity score and histology. Similar results were obtained by Thomas et al[25] and Itoh et al.[31] These authors, however, stressed that US elastography has limitations, including the difficulty of assessing lesions that are not surrounded by sufficient normal tissue or located in the retroareolar area, where pressure cannot be exerted evenly. In addition, there was a certain degree of subjectivity when assigning the elasticity score, making the examination operator-dependent. Indeed, the extent of tissue compression influences the elasticity image and, consequently, the elasticity score. Endoscopic elastography has been used to differentiate between benign and malignant pancreatic masses and lymph nodes.[29,32] In recent years transient elastography (Fibroscan) has also been applied for non-invasive evaluation of tissue elasticity of the liver in patients with hepatic fibrosis[33]and in the clinical evaluation of musculoskeletal pathology.[34]

CONVENTIONAL US

Fujimoto et al in 1967 were the first to describe detection and characterization of thyroid nodules by US.[35] From then on, several studies have been designed in order to establish the validity of thyroid US in the diagnosis of benign and malignant thyroid nodules. Moreover, the rapid development of US equipment during recent years, with the availability of 7–13-MHz high-frequency transducers, has allowed the detection of very small thyroid lesions (2–3 mm). Non-palpable thyroid nodules are detected by US in 13–50% of the general population[4,36], raising the question of which nodules warrant evaluation by FNA. In a prospective study[37] carried out in apparently thyroid-disease-free subjects living in an area of borderline iodine sufficiency, small colloid lumps were detected in 37/482 subjects (7.7%), and ten of these vanished during a follow-up of 5 years. Thyroid nodules, defined as solid, mixed or cystic lesions each surrounded by a well-defined capsule, were found in 27 of the 482 subjects (5.6%) included in the study. Cytology excluded malignancy in all nodules chosen for FNA for the presence of suspicious echographic patterns. As observed by other authors[4,36], the prevalence of thyroid nodules increased with age, and was higher in females older than 35 years and in subjects with an enlarged thyroid. During the 3-year follow-up among the 27 subjects in whom thyroid nodules were detected by ultrasound, an increased number of nodules was found in eight subjects and a significant increase in nodule volume in five.[37] This study confirms that thyroid US reveals the presence of thyroid nodules in a significant proportion of apparently thyroid-disease-free

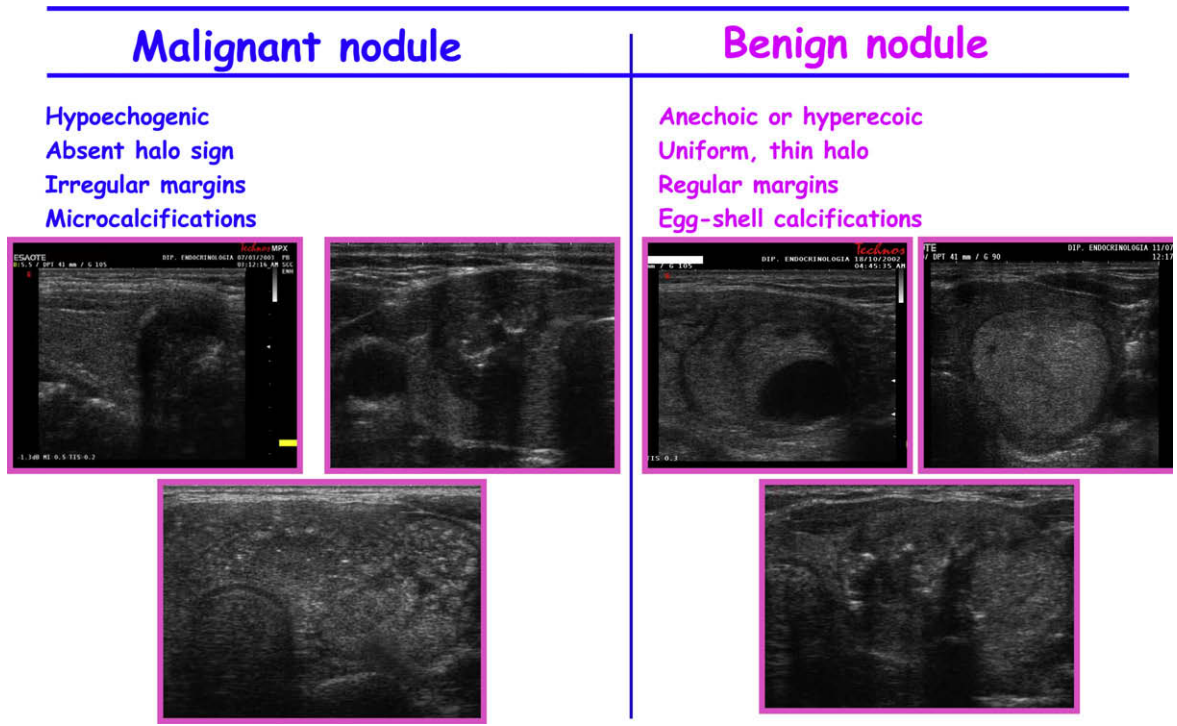

Figure 1. Ultrasound (US) patterns in thyroid nodules.

subjects living in a borderline iodine-sufficient urban area, and stresses the importance of defining US criteria for the selection of nodules that warrant FNA cytology.

The echographic patterns more frequently associated with thyroid carcinoma are hypoechogenicity of the nodule with respect to surrounding parenchyma, the absence of halo sign and the presence of microcalcifications (Figure 1).[38–41] However, it is widely recognized that any single echographic pattern cannot be considered specific for malignancy. In a prospective study[14] carried out in 104 patients with cold thyroid nodules who underwent surgery for the suspicion of malignancy at FNA or for the size of the nodule, the absence of halo sign was observed in 66% of carcinomas and in 23% of benign nodules, and was the single pattern most predictive of malignancy. The combination of absent halo sign/presence of microcalcifications was found to have a higher specificity with respect to single patterns, but a lower sensitivity (26%). An increased intranodular vascularization, which has been reported as a sign of malignancy, in our experience had a low predictive value. The combination absent halo sign/presence of microcalcifications and increased intranodular vascularization was strongly associated with malignancy. While the specificity of this combination was very high (97%), the sensitivity was very low (17%), being observed in only 5/30 carcinomas (Table 1).

Papini et al[15,42] performed ultrasound-guided FNA on 402 consecutive patients with non-palpable thyroid nodules measuring 8–15 mm. Non-palpable nodules were selected for FNA on the basis of US patterns previously described: i.e., hypoechogenicity, solid aspect, absence of halo sign, presence of microcalcifications, and intranodular blood flow. Thyroid malignancy was found in 18/195 solitary thyroid nodules (9.2%) and in 13/207 nodules present in a multinodular goitre (6.3%). In this series TNM staging demonstrated extra capsular growth in 35.5% and nodal involvement in 19.4%. The conclusion of this paper is that non-palpable thyroid lesions showing US features suspicious for malignancy should be evaluated by FNA. Leenhardt et al[43] underline the indications and limits of US-guided cytology in non-palpable thyroid nodules. No correlation between the size and carcinoma on histology was found. The solid hypoechoic pattern was significantly correlated with malignancy. The adequacy of material obtained by FNA was correlated with the size of the nodule, the number of inadequate results being more frequent in nodules <1 cm.

The American Society of Radiologists in Ultrasound[17] has recently reviewed US patterns associated with cancer in thyroid nodules (Table 2). In particular, US features associated with malignancy were microcalcifications, hypoechogenicity, irregular margins or absent halo sign, solid pattern, intranodular vascularization, and shape (taller than wide). All these patterns taken singly do not have sufficient predictive value. When multiple patterns suggestive of malignancy are simultaneously present in a nodule the specificity increases but the sensitivity becomes unacceptably low. However, in

Table 1. Echographic patterns and histology in 104 patients with thyroid nodule.

US patterns	Carcinoma (n = 30)	Benign (n = 74)	*P*	Specificity (%)	Sensitivity (%)
Halo-/Microcal IBF	5	2	<0.01	97.2	16.6
Halo-/Hypoech IBF	13	6	<0.0001	91.8	43.3
Hypoech/Microcal IBF	6	8	<0.20	89.1	20

US, ultrasound; Halo-, absent halo sign; Microcal, microcalcifications; Hypoech, hypoechogenicity; IBF, intranodular blood flow. Modified from Rago et al (1998, *European Journal of Endocrinology* **138**: 41–46) with permission.

Table 2. Ultrasound signs suggestive of malignancy.

US patterns	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Microcalcifications[14,15,38–40]	6.1–59.1	85.8–95.0	24.3–70.7	41.8–94.2
Hypecogenicity[14,15,38–40]	26.5–87.1	43.4–94.3	11.4–68.4	73.5–93.8
Irregular margins or no halo sign[40]	17.4–77.5	38.9–85.0	15.6–27.0	88.0–92.1
Solid[39–41]	26.5–87.1	43.4–94.3	11.4–68.4	73–93.8
Intranodular vascularity[14,15,39–41]	54.3–74.2	78.6–80.8	24.0–41.9	85.7–97.4
Taller than wide[39]	32.7	92.5	66.7	74.8

PPV, positive predictive value; NPV, negative predictive value.

a recent consensus on the diagnosis of thyroid nodular disease it has been agreed that thyroid US is essential to select the nodules that warrant FNA.[17–20]

If thyroid nodules are present, US examination should be extended to the neck lymph nodes. Metastatic lymph nodes appear as rounded, solid with absence of the hyperechoic striae corresponding to the hilus, or cystic. Sometimes the pattern is solid and inhomogeneous, with spot calcifications (Figure 2).

Practice points

- in thyroid nodules, US features associated with malignancy are microcalcifications, hypoechogenicity, irregular margins or absent halo sign, solid aspect, intranodular vascularization and shape (taller than wide)
- these patterns taken singly are poorly predictive
- when multiple patterns suggestive of malignancy are simultaneously present the specificity of US increases, the sensitivity decreases
- neck lymph nodes: metastatic lymph nodes appear rounded, solid with absence of the hyperechoic striae corresponding to the hilus, or cystic

US ELASTOGRAPHY

Description of the technique and basic principles

Elastography is a newly developed US technique that has recently been applied in the diagnostic approach of nodular thyroid disease. The basic principle of elastography is that tissue compression produces strain (displacement) within the tissue that is smaller in harder than in softer tissues, and is scored by measuring the degree of distortion of the US beam under the application of an external force. Tissue elasticity was initially measured by an off-line processing of US images obtained before and after compression by the probe, but this technique is cumbersome and time-consuming.[44] More recently, methods assessing real-time measurement of tissue strain were developed: i.e. the spatial correlation method, the phase-shift tracking method, and the combined

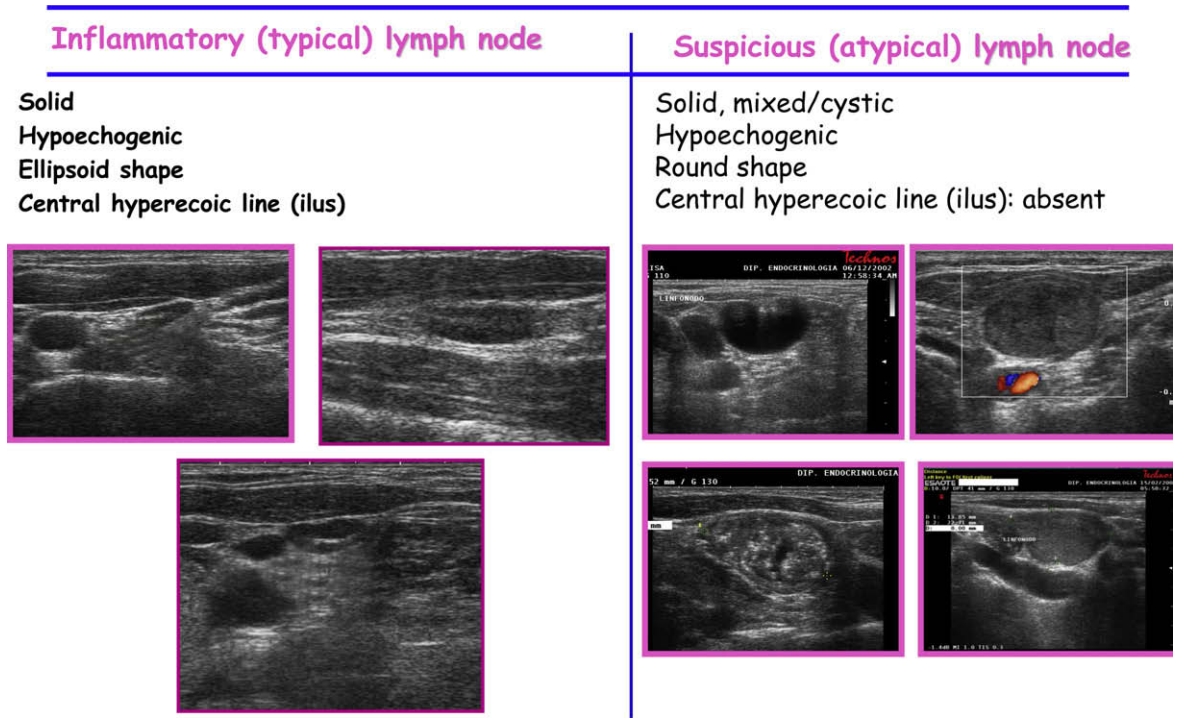

Figure 2. Ultrasound (US) patterns in lymph nodes.

Table 3. Advantages and disadvantages of ultrasound elastography (USE).

Method	Advantages	Disadvantages	Precision
Spatial correlation	Displacement two dimensions: longitudinal, lateral	Lengthy	Moderate
Phase-shift tracking	Precise longitudinal tissue motion	Fails to measure large displacement	High
Combined autocorrelation CAM	Rapid and accurate detection of longitudinal displacement	None	High
Off-line processed	Quantitative measure of stiffness	Labour-intensive and time-consuming	

autocorrelation method (CAM). Each method appears to have advantages and disadvantages (Table 3). The spatial correlation method is used to demonstrate displacement in two dimensions (longitudinal and lateral), but the processing speed is very slow, which is a disadvantage for real-time assessment. The phase-shift tracking method is based on an autocorrelation method that is well known as a principle of colour Doppler ultrasonography. It precisely determines longitudinal tissue motion, but poorly compensates for movements in the lateral direction, which is a disadvantage for free-hand compression. The more recently developed CAM can compensate for up to about 4 mm of lateral slip.[45,46]

With the CAM method, US elastographic measurements are performed during the US examination, using the same real-time instrument and the same probe. The probe is placed on the neck, a light pressure is exerted, and a box which includes the nodule to be evaluated is selected by the operator. The principle of US elastography is to acquire two ultrasonographic images (before and after tissue compression by the probe), and to track tissue displacement by assessing the propagation of the beam. The CAM dedicated software is able to provide an accurate measurement of tissue distortion. The US elastogram is displayed over the B-mode image in a colour scale that ranges from red/green for components with greatest elastic strain (i.e. the softest components) to blue for those with no strain (i.e. the hardest components). The US elastographic image is matched with an elasticity colour scale and classified by using the elasticity score of Ueno and co-workers (Figure 3).[47] To minimize the inter- and

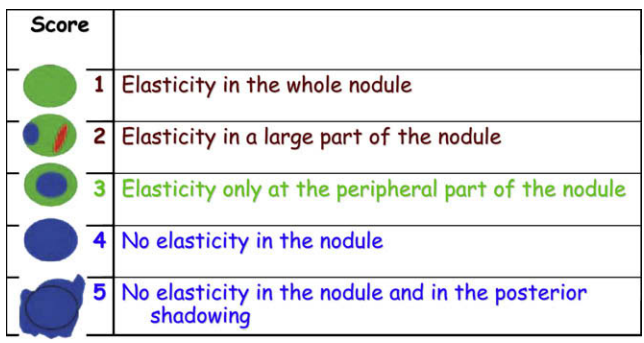

Figure 3. Elasticity score.[47].

intra-observer variability, the freehand compression applied on the neck region is standardized by real-time measurement displayed on a numeric scale to maintain an intermediate level optimal for US elastographic evaluation. It is important that the level of pressure is kept constant throughout the examination. This technique is easy to perform and requires no more than 3–5 minutes of additional examination time. Static and moving images are also recorded to be reviewed.

Practice points

- elastography is a newly developed US technique that has recently been applied in the diagnostic approach of nodular thyroid disease as indicator of malignancy
- the US elastogram is displayed over the B-mode image in a colour scale: red/green for components with greatest elastic strain (i.e. the softest components), blue for those with no strain (i.e. the hardest components)

Results

Fukunari[48] investigated the clinical usefulness of real-time elastography in three patients with thyroid cancer. In one case of papillary carcinoma the elastography showed a pattern characterized by a mottled blue mixed with a light green; in the second case the papillary carcinoma was in the solid part inside a cyst that appeared hyperechoic in B-mode and was visualized as completely blue hard tissue by elastography. In the third case, a follicular cancer with vascular invasion, the peripheral zone of the tumour was displayed in blue and the centre in light green. An adenomatous goitre showed a light green colour up to the periphery. Lyshchik et al[44] studied 31 patients with nodular goitre, using both a real-time elastography on an adapted US scanner and an off-line processing of strain images reconstructed from radiofrequency data stored during US examination. The authors found that the strain index value, obtained by off-line processed elastograms, was the strongest independent predictor of malignancy. This criterion had 96% specificity and 82% sensitivity. Two other elastographic criteria, which were evaluated on real-time elastograms, had low sensitivity. Thus, only with the off-line processing it was possible to compare the stiffness of benign and malignant lesions for the differential diagnosis of thyroid cancer. However, this method is labour-intensive and time-consuming.[44]

Rago et al[49] have employed in a larger group of patients the newly developed US apparatus by which the freehand compression applied in the neck region was standardized by real-time measurement on a numerical scale, rendering the real-time determination of tissue elasticity highly reproducible. The study included 92 consecutive patients with a single thyroid nodule who underwent surgery for compressive symptoms or suspicion of malignancy on FNA. The agreement on the scoring of US parameters was $>90\%$ between two observers. In particular, scoring by the two examiners coincided in 83/92 patients. In nine cases the final score was agreed after joint re-examination of the recorded movies. The indications for surgery were the size of nodules in patients with cytology of benign lesion ($n = 25$), an indeterminate ($n = 32$) or non-diagnostic cytology ($n = 13$), a cytological diagnosis suggestive ($n = 15$) or suspicious ($n = 6$) of papillary carcinoma, and medullary carcinoma in one case. On US

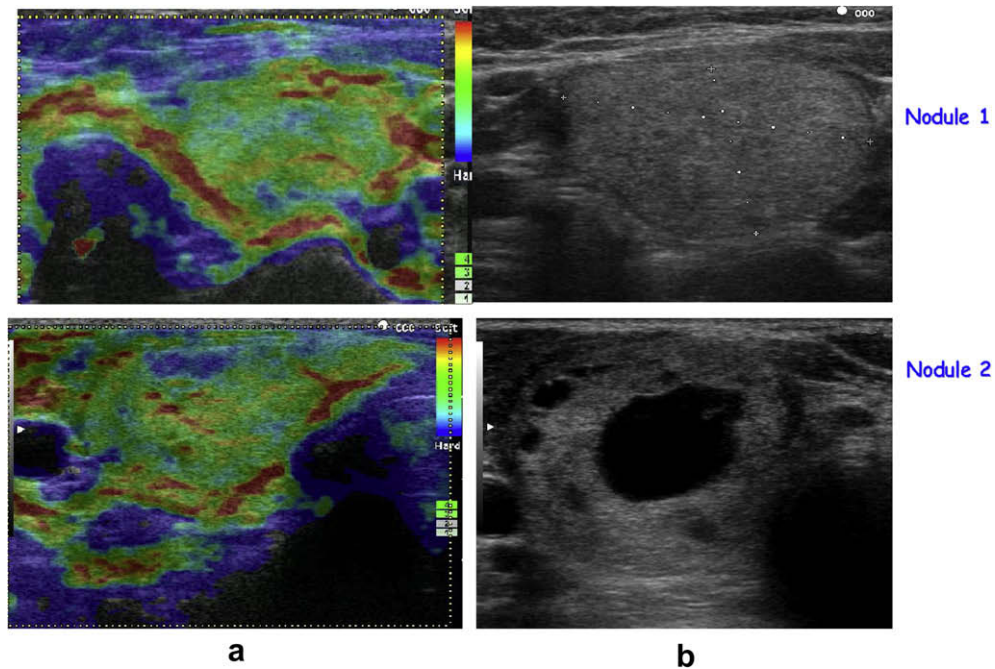

Figure 4. (a) Ultrasound (US) elastography, and (b) conventional US of thyroid nodule with an elasticity score of 1.

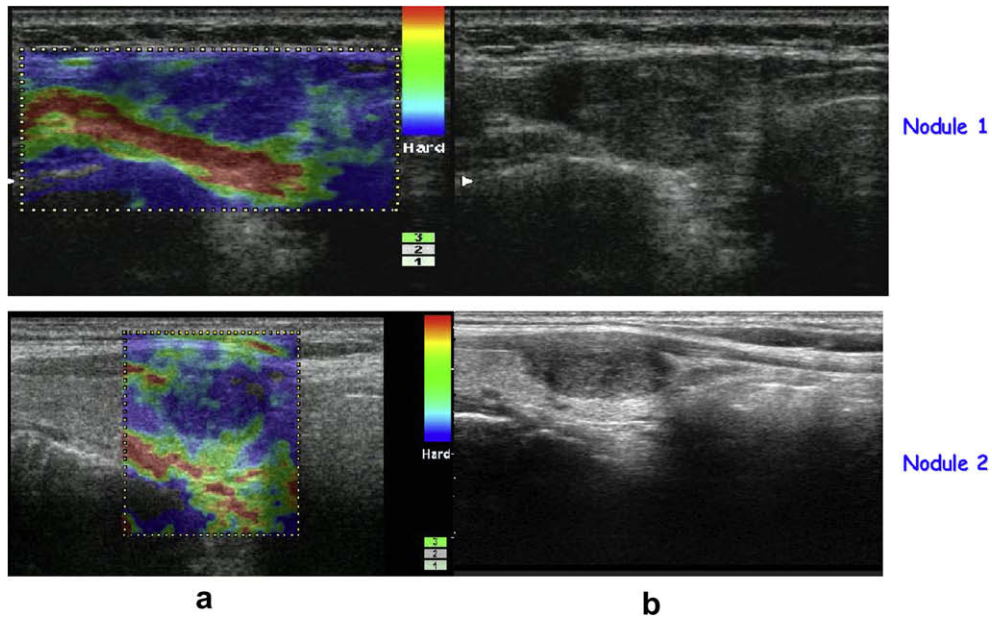

Figure 5. (a) Ultrasound (US) elastography, and (b) conventional US of thyroid nodule with an elasticity score of 5.

Table 4. Predictive value of real-time ultrasound elastography (USE) in 92 patients with benign nodules or carcinoma on histology.

Score	Total	Benign (n)	Carcinoma (n)	Sensitivity (%)	Specificity (%)
1–2	49	49	0		
3	13	12	1		
4–5	30	0	30	97	100
Total	92	61	31		

Modified from Rago et al (2007, *Journal of Clinical Endocrinology and Metabolism* **9**: 2917–2922) with permission.

elastography 41 cases scored 1 (all benign lesions); eight cases scored 2 (all benign); 13 cases scored 3 (one carcinoma and 12 benign); 16 cases scored 4 (all carcinomas); and 14 cases scored 5 (all carcinomas) (Figures 4 and 5). Thus, all 61 cases with a final diagnosis of benign nodule had a score 1–3, while 30/31 (96.7%) with a final diagnosis of carcinoma had a score 4–5 ($P < 0.0001$). One out of 31 nodules (3.3%) with the histological diagnosis of papillary cancer had a score of 3. Thus, the US elastography displayed a sensitivity of 97%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 98% (Table 4). The predictivity of US elastographic measurement was independent of the nodule size, high sensitivity and specificity being observed also in nine nodules which had the largest diameter – between 0.8 and 1 cm –submitted to surgery for an FNA result suggestive or suspicious of papillary thyroid cancer (five cases) or indeterminate lesion (four cases) (Table 5). Five of these nine nodules had scores of 4–5, and in all of them the histological diagnosis of carcinoma was confirmed. In four nodules the elasticity score was 1–3 and the histological diagnosis was follicular adenoma in three cases and hyperplastic nodule in one case. Thus, the possibility of selecting the area of US elastography analysis allowed a correct scoring even of these small nodules independently from their position within the thyroid lobe. When the data were analysed by logistic regression, the elastographic score was an independent predictor of the final histological diagnosis, as the score 4–5 was in all cases but one coincident with the diagnosis of cancer. Both the absent

Table 5. Predictive value of real-time ultrasound elastography (USE) according to the nodule size in 92 patients with benign nodules or carcinoma on histology.

Size	Score	Benign	Carcinoma (n)	Sensitivity (%)
0.8–1 cm	1–3	4	0	100
	4–5	0	5	
1.1–2 cm	1–3	15	0	100
	4–5	0	16	
>2 cm	1–3	42	1	90
	4–5	0	9	
All	1–3	61	1	97
	4–5	0	30	

Modified from Rago et al (2007, *Journal of Clinical Endocrinology and Metabolism* **9**: 2917–2922) with permission.

Table 6. Predictive value of real-time ultrasound elastography in 32 patients with indeterminate lesion on cytology and final histological diagnosis of benign nodules (n = 25) or carcinoma (n = 7).

Score	Total	Benign (n)	Carcinoma (n)	Sensitivity (%)	Specificity (%)
1–3	26	25	1		
4–5	6	0	6	72	97
Total	32	25	7		

Modified from Rago et al (2007, *Journal of Clinical Endocrinology and Metabolism* **9**: 2917–2922) with permission.

halo sign and the presence of spot microcalcifications were independently associated with the elastographic score 4–5. Among the 32 patients with an FNA result of indeterminate (follicular) lesion, 25 had a benign follicular adenoma on histology and seven a carcinoma: one papillary, classic variant; four papillary follicular variant; two minimally invasive follicular carcinoma. Conventional US, as previously shown in a larger series of patients[50], was not predictive in these patients. At variance with this, a US elastography score of 4–5 was observed in six out of seven (86%) patients with carcinoma, and a score of 1–3 in all the 25 patients with benign lesions (Table 6). In four patients with nodules showing a calcified shell, the US elastogram was not valuable, since the ultrasound beam does not cross the calcifications and no tissue strain was obtained by the probe pressure. Similarly, US elastogram results were considered unreliable in four patients with completely cystic nodules, since nodule elasticity was dependent on the liquid content and not on the solid wall. Thus, nodules showing these US characters are not suitable for evaluation by US elastography. An extension of number of patients to 161 patients has confirmed the above results with a sensitivity of 83% and a specificity of 97%.

Two reports were recently published on the comparison between results obtained with elastography and FNA. Tranquart et al[51] examined 108 nodules from 96 consecutive patients. None of the 95 nodules classified as score 1–2 had malignancy on FNA, while six were malignant and two were indeterminate on FNA out of the 13 with a score 3–4. In the series of Asteria et al[52], 16/17 nodules (94%) classified as score 3–4 were carcinomas. Of benign nodules, 50/69 had a pattern 1–2, and 13/69 had a 3–4 pattern. One carcinoma had a score of 2. These data, although obtained in smaller numbers of patients and by comparing US elastography with FNA rather than histology, confirm the data of Rago et al.

Practice points

- Lyshchik et al[44] found that off-line processed elastography was the strongest independent predictor of malignancy in thyroid nodules with a specificity of 96% and sensitivity of 82%; this method is labour-intensive and time-consuming
- Rago et al[49] studied 92 consecutive patients with a single thyroid nodule who underwent surgery for compressive symptoms or suspicion of malignancy on FNA, using real-time elastograms; the US elastography had a sensitivity of 97%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 98%. The predictivity of US elastographic measurement was independent of the nodule size and was confirmed also in an indeterminate (follicular) lesion on FNA

CONCLUSIONS

Thyroid ultrasound (US) is a widespread technique that is used as a first-line diagnostic procedure for detecting and characterizing nodular thyroid disease. US features associated with malignancy are microcalcifications, hypoechogenicity, irregular margins or absent halo sign, solid aspect, intranodular vascularization, and shape (taller than wide). All these patterns taken singly are poorly predictive. When multiple patterns suggestive of malignancy are simultaneously present in a nodule, the specificity of US increases but the sensitivity becomes unacceptably low. In a recent consensus it has been agreed that thyroid US is essential to select the nodules to be submitted to FNA.

Free-hand US elastography appears to be a new powerful diagnostic tool for thyroid nodules. The predictivity of US elastography was shown to be independent of the nodule size, high sensitivity and specificity being observed also in nodules <1 cm, independently from the position of the nodule within the thyroid lobe. Available data suggest that US elastography is the best available non-invasive tool for the evaluation of thyroid nodules, comparable to FNA. However, it is important to note that the paper that includes the largest number of patients with final histological diagnosis was performed with selected patients in whom thyroid surgery had been already planned because of cytological suspicion or large nodular size. This could represent a bias that amplifies the predictive value of US elastography. Results were, however, confirmed in other series which included unselected patients in whom the diagnosis of benign or malignant was performed on cytology.

In follicular lesions conventional echographic patterns were found to be of minor relevance for predicting carcinoma. The predictivity of US elastography in this subgroup of patients was highly rewarding, scores of 4–5 being found in all but one patients having a final diagnosis of malignancy and 1–3 in all the patients with a histological diagnosis of a benign lesion.

Conventional US retains pivotal importance in defining which nodules are suitable for US elastographic characterization. Indeed, nodules in which US reveals the presence of a calcified shell have to be excluded from the US elastographic evaluation. Similarly, in cystic nodules US elastography cannot give useful information. One other limitation is that the nodule to be examined must be clearly distinguishable from other nodules present in the thyroid. Thus, multinodular goitres with coalescent nodules are not suitable for this analysis.

US elastography seems to have great potential as a new tool for the diagnosis of thyroid cancer, especially in nodules with indeterminate cytology. Larger prospective studies are needed to confirm these results and to establish the diagnostic accuracy of this technique.

Practice points

- USE is a powerful new diagnostic tool that assesses hardness as an indicator of malignancy in thyroid nodules. USE has a high specificity and sensitivity independent of the nodule size, this predictive value being maintained in follicular lesions. Available data suggest that USE is the best available non-invasive tool comparable to FNA for the evaluation of thyroid nodules, provided that the nodule is solid and devoid of coarse calcifications. Thus conventional US retains importance for selection of nodules in which USE is predictive
- USE has great potential as a new tool for the diagnosis of thyroid cancer, especially in nodules with indeterminate cytology

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